Rule 1.126

99. (New) The method according to claim 54 wherein the heat shock protein preparation is administered to the subject in an amount effective to induce or increase an immune response in the subject to the component.

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REMARKS

Claims 4, 9, 13, 17, 21, 25-42, 44, and 46-65 will be pending upon entry of this reply. Applicant has hereinabove amended claims 4, 13, 17, 21, 25, 42, and 44, and added new claims 48-65 to clarify that which Applicant regards as the invention. Support for the amendment to claim 4 can be found at page 12, lines 32-36. Support for the amendments to claims 13, 17, 21, 54, 55, and 56 can be found throughout the specification as filed. Support for the amendment to claim 25 can be found in the specification as filed as page 15, lines 14-16. Support for the amendment to claim 42 can be found in the specification as filed at page 31, line 26. Support for new claims 48 and 49 can be found in the specification as filed at page 15, lines 27-29. Support for new claims 50-51 can be found in the specification as filed at page 31, line 19. Support for new claim 52 can be found in the specification as filed at page 31, line 26. Support for new claims 53 and 54 can be found at page 31, line 30 through page 32, line 7. Support for new claims 55-57 can be found in the specification as filed at page 14, line 32 through page 15, line 1. Support for new claim 58 can be found in the specification as filed at page 9, line 26 and page 15, lines 13-15. Support for new claims 59-65 can be found in the specification as filed at page 8, lines 15-24. No new matter is added. A clean version of all pending claims as amended herein is attached hereto as Exhibit B for the convenience of the Examiner.

THE INDEFINITENESS REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claim 44 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Specifically, the Examiner states that claim 44 is unclear in its recitation of the term "leukemias" in that it is unclear whether the claim limits the leukemias to the ones listed in the claim or whether there are others not listed but also encompassed by the term. Office Action at page 2. Applicant has amended the claim so as to more particularly point out the claimed invention and submits that the rejection is thereby rendered moot.

The Examiner also states that claim 44 is indefinite in its recitation of the term "heavy chain disease." Specifically, the Examiner contends that the metes and bounds of the term "heavy chain disease" are unclear because the specification does not provide an adequate description of the diseases which are encompassed by the term. Office Action at page 3. Applicant respectfully reminds the Examiner that primary purpose of definiteness of claim language is to ensure that the scope of the claims is clear to one skilled in the pertinent art. Applicant submits that one skilled in the art would recognize that heavy chain diseases encompass a group of diseases, the paraproteinemias, characterized by production of homogenous immunoglobulins or fragments, and associated with malignant disorders of the plasmacytic and lymphoid cell series. As evidence of the foregoing, the Examiner's attention is invited to Stedman's Medical Dictionary, 497-498 (26th Edition 1995), attached hereto as Exhibit C, which recites the definition of "heavy chain disease."

THE ENABLEMENT REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

Claims 4, 9, 13, 17, 21, 25-42, 44, and 46-47 are rejected under 35 U.S.C.

§ 112, first paragraph, as not enabled by the specification. The Examiner states that while the specification is enabling for eliciting an immune response through the administration of heat shock proteins in combination with a cancer cell antigenic component, the specification does not reasonably provide enablement for treatment and prevention of cancer in humans through the co-administration of a vaccine and heat shock proteins. Office Action at page 3.

In particular, the Examiner alleges that "no where [sic] in the art does it show that HSPs are effective at treating or preventing disease in humans, especially cancer" (emphasis added) (Office Action at page 4), "the combination of a vaccine . . . and a HSP has not been shown in the art to be effective in the prevention of cancer" (emphasis added) (Office Action at page 5) and "because the art teaches that efficacy of cancer vaccines is highly unpredictable, it would require undue experimentation by one of skill in the art to be able to practice the invention commensurate in scope with the claims" (emphasis added) (Office Action at page 5).

In response, the Applicant respectfully submits that the Examiner has not met the necessary burden that the Patent and Trademark Office bears in establishing a *prima facie* case of non-enablement.

Preliminarily, Applicant wishes to state the legal standard set forth by the Federal Circuit in *Brana* for compliance with 35 U.S.C. § 112, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995) (emphasis in the original). Under 35 U.S.C. § 112, a patent applicant's specification which contains a teaching of how to make and use the invention must be taken as enabling unless the Patent and Trademark Office provides sufficient reason to doubt the accuracy of the

disclosure. *In re Marzocchi*, 169 U.S.P.Q. 367, 369-70 (CCPA 1971); *see also* MPEP 2164.02.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Teletronics Inc.*, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). Factors to be considered in determining whether an amount of experimentation is undue include: the guidance provided by the specification, the presence of working examples, the breadth of the claims, the amount of pertinent literature and the level of skill in the art. *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988); *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). It should be noted that while the predictability of the art can be considered in determining whether an amount of experimentation is undue, mere unpredictability of the result of an experiment is not a consideration. *In re Angstadt*, 190 U.S.P.Q. 214, 219 (C.C.P.A. 1976).

Furthermore, the law does not require the scope of enablement provided by the specification to mirror precisely the scope of protection sought by the claims. *See In re Fisher*, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970); *see also In re Wright*, 27 U.S.P.Q.2d 1510 (Fed. Cir. 1993). To be enabled, all the law requires is that the scope of enablement provided by the specification bear a "reasonable correlation" to the scope of the claims. *Id.* The burden of proving that the enabled examples do not reasonably correlate with the scope of the proposed claims is on the Examiner.

The Federal Circuit has emphasized that the burden is on the Examiner to present evidence that those of skill in the art would doubt the disclosure. In *Brana*, the Federal Circuit held that "Applicants should not have to be required to substantiate their

presumptively correct disclosure to avoid a rejection under the first paragraph of § 112. *In re Brana*, 34 U.S.P.Q.2d at 1441, citing *In re Marzocchi*, 169 U.S.P.Q. at 369-70 (CCPA 1971).

The Full Scope of the Present Claims Is Enabled by the Specification

Applicant respectfully submits that the legal standard for enablement has been met in this case. In particular, Applicant respectfully asserts that no undue experimentation is required to treat or prevent cancer in a subject through the co-administration of a cancer vaccine in combination with an HSP preparation as set forth in the claims given the guidance provided in the present specification and knowledge in the art. Moreover, the Examiner has not met his burden in presenting evidence that would lead a person of ordinary skill in the art to conclude that the present methods of treating or preventing cancer through the co-administration of a vaccine in combination with an HSP preparation as set forth in the claims would require undue experimentation.

Applicant respectfully directs the Examiner's attention to Reference BE (made of record in the revised form PTO-1449 filed on July 1, 2002), entitled "Exogenous heat shock proteins provide adjuvant effects on enhancing the immunogenicity of apoptotic tumor cells and inducing anti-tumor immunity," AACR 93rd Annual Meeting, April 6-10, 2002, Vol. 43, #2214, by H. Feng *et al.* ("Feng *et al.*").

Feng *et al.*, a post-filing date reference, corroborates the teachings of the instant specification. Feng *et al.* demonstrates preventative effectiveness. Feng *et al.* reports that 100% of mice immunized with a cancer vaccine (FasDD-induced apoptotic 12B1-D1 leukemia cells) combined with an HSP preparation which does not display the

immunogenicity of the tumor (FS-IEFcc[1] from naïve mouse liver), that are subsequently challenged with a LD100 dose of tumor cells, reject the tumor challenge.

Feng *et al.* also reports therapeutic effectiveness. Mice inoculated with an LD100 dose of tumor cells (12B1-D1 tumor cells) which are subsequently treated with a cancer vaccine (mitomycin C induced 12B1-D1 apoptotic tumor cells) combined with an HSP preparation which does not display the immunogenicity of the tumor (FS-IEFcc), showed tumor development which progressed significantly slower than tumor development in mice which were innoculated with an LD100 dose of tumor cells (12B1-D1 tumor cells) and then treated with a cancer vaccine (mitomycin C induced 12B1-D1 apoptotic tumor cells) combined with a control (saline).

Applicant also respectfully directs the Examiner's attention to Reference CP (made of record in revised form PTO-1449 filed herewith), entitled "Exogenous stress proteins enhance the immunogenicity of apoptotic tumor cells and stimulate antitumor immunity" 2003, Blood 101(1): 245-252 by Feng *et al.* ("Feng II").

Feng II, a post-filing date reference, also corroborates the teachings of the instant specification. Feng II reports that mice injected with a cancer vaccine (AP20187-induced apoptotic 12B1-D1 tumor cells) combined with an HSP preparation which does not display the immunogenicity of the tumor (hsp70 devoid of tumor specific antigenic peptides) significantly delayed tumor growth compared with mice that were injected with the cancer vaccine (AP20187-induced apoptotic 12B1-D1 tumor cells) alone. See Feng II at page 247, first paragraph and Figure 1A.

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[1] Free solution/isoelectric focusing enriched multiple HSP (or chaperone complexes).

Taken together, the results in Feng *et al.* and Feng II corroborate the teachings of the specification that HSP adjuvant vaccine therapy is prophylactically and therapeutically effective and useful. In sum, Feng *et al.* and Feng II corroborate the teachings of the specification that the administration of a vaccine composition that displays the immunogenicity of a component against which an immune response is desired in conjunction with an HSP that does not display the immunogenicity of the component would be useful in treating or preventing cancer.

Further, the Examiner's non-enablement argument is unsound as the specification adequately teaches co-administration of an HSP and vaccine composition to treat or prevent cancer in a subject and provides considerable guidance and direction to practice the claimed invention.

Moreover, the specification provides detailed guidance to one of skill in the art seeking to carry out the methods of the invention. In particular, the specification teaches various vaccine compositions that can be used in the methods of the invention, *e.g.*, vaccines containing tumor specific or tumor-associated antigens (specification at page 31, line 26), HSPs that may be used in the methods of the invention (specification at page 17, lines 34-36), methods of preparing and purifying HSPs and HSP complexes (specification at page 21, line 4 through page 31, line 11), patients (specification at page 32, lines 19-24), dosages of HSP preparations (specification at page 34, lines 9-22), timing regimens (specification at page 34, lines 23-32), dosages of vaccine composition (specification at page 34 line 33 through page 35, line 5), considerations when selecting a site of administration (specification at page 35, lines 6-16), routes of administration (specification at page 35, line 17-26), buffers (page 35, lines 33- page 36, line 6), and formulations for numerous methods of administration (specification at page 36, lines 32 through page 37, line 35). The teachings provided therein

would enable a skilled artisan to practice the invention claimed herein without undue experimentation.

Additionally, the specification provides explicit guidance to one of skill in the art seeking to monitor the immune response elicited by the claimed methods. Specifically, the specification teaches one how to make a determination of the generation of immunogenic responses by administration of vaccines in conjunction with HSP. Specification at page 39, line 29. The assays described therein include ELISA assays, tetramer staining assays, mixed lymphocyte target culture assays, and ELISPOT assays. *See* specification at page 39, line 29 through page 42, line 37.

Indeed, the Examiner acknowledges that the specification describes the use of HSPs and their interaction with APCs in the generation of an immunogenic response and the role HSPs play as adjuvants in the generation of immune responses. However, the Examiner contends that the specification contains no working examples that teach one of skill in the art how to make and use HSPs with vaccines to prevent the occurrence of cancer. In response, Applicant respectfully points out that there is no absolute statutory requirement for a working example if the disclosure is such that one of skill in the art can practice the claimed invention. *In re Borkowski*, 164 U.S.P.Q. 642 (CCPA 1970). The number and variety of working examples is irrelevant if the disclosure is "enabling."

Although the Examiner acknowledges that the art teaches that HSPs are effective in the treatment of cancer <u>in mice</u> through generation of immunogenic response to the HSP and its associated peptide complex, the Examiner maintains that "no where [sic] in the art does it show that HSPs are effective at treating or preventing disease <u>in humans</u>, especially cancer." Office Action at page 4 (emphasis added).

In response, Applicant respectfully submits that the Examiner has misconstrued the legal standard for enablement and directs the Examiner's attention to the discussion of Feng *et al.*, *supra*, and the appropriate legal standard set forth below with regard to enablement, and specifically enablement in light of proven efficacy in standard experimental animals.

To satisfy the enablement requirement, an applicant need not provide direct evidence of efficacy in humans simply because the claims encompass *in vivo* administration to humans. The standard articulated by the Federal Circuit is that of whether "one skilled in the art would accept the model as reasonably correlating to the condition." *In re Brana*, 34 U.S.P.Q.2d 1436, 1441 (Fed. Cir. 1995). Additionally, the Federal Circuit in *In re Brana* has specifically addressed whether "reasonable correlation" exists where a specification sets forth working examples, specifically murine studies showing certain pharmaceutical compounds were effective anti-tumor chemotherapeutic agents, but the application's claims encompass broader human applications. *In re Brana*, 34 U.S.P.Q.2d at 1441. In ultimately finding that *in vivo* chemotherapeutic data from testing in animals sufficiently met Section 112, first paragraph's enablement requirement to support the claimed anti-tumor chemotherapeutic compositions for use in humans, the court held "proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility." *In re Brana*, 34 U.S.P.Q.2d at 1442. Applicant submits that the immunotherapy murine studies carried out in Feng *et al.* confirm that the present claims, which encompass human applications, are fully enabled.

The Examiner further maintains that the "efficacy of cancer vaccines is highly unpredictable." Office Action at page 5, citing Evans as evidence of such unpredictability of the art. Applicant respectfully disagrees.

In quoting Evans, the Examiner reiterates a portion of the summary which presents an overview of the future of cancer vaccines, "the notion that cancer vaccines will replace standard therapeutic strategies in malignant disease still belongs to the realm of fiction" (emphasis added). Applicant respectfully points out that the present invention does not claim necessarily to replace standard therapeutic strategies. The methods of the present invention may be used in combination with and/or may complement standard therapeutic strategies, such as surgery and chemotherapy. Additionally, the methods of the present invention increase the efficacy and/or efficiency of cancer vaccines, thereby strengthening the therapeutic and prophylactic value of cancer vaccines as a whole.

Moreover, contrary to the Examiner's characterization of the teachings of Evans, Applicant respectfully points out that Evans takes a very favorable view of cancer vaccines. On page 302, column 1, lines 11-12, in the first paragraph of the section entitled "Cancer vaccines: potential clinical applications", and on page 303, column 1, lines 18-27, Evans and Kaye refer to clinical trials which are not only encouraging with regard to the effectiveness of cancer vaccines, they also demonstrate the "safety of this approach." The gist of the authors' view on the therapeutic use of cancer vaccines is given in the last paragraph of their article, "The notion that the immune system can be activated by cancer vaccines to attack and reject established tumor is a fact." On balance, Evans supports the efficacy of cancer vaccines.

Accordingly, in view of the foregoing, Applicant respectfully submits that the Examiner's rejection of claims 4, 9, 13, 17, 21, 25-42, 44, and 46-47 is obviated and/or overcome and request that the rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 102 SHOULD BE WITHDRAWN

Claims 4, 9, 13, 27, 30, 33, 42, 44, and 46 are rejected under 35 U.S.C. 102(a) as anticipated by Chen *et al.*, 2002, *Cancer Res.* 60(4): 1035-1042. Specifically the Examiner states that Chen *et al.* teaches a "DNA-based vaccine fused to a HSP effective in the reduction of tumor burden in mice." Office Action at page 6. Applicant respectfully disagrees that this teaching is sufficient to render Chen *et al.* anticipatory.

According to applicable case law, a claim is anticipated only if each and every element set forth in the claim is found in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987). There must be no difference between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991).

Applicant submits that Chen *et al.* does not teach every element of the invention claimed herein. Chen *et al.* describes a method for increasing the efficacy of a DNA vaccine, in particular, DNA encoding human papillomavirus type 16 E7, by fusing the DNA to Mycobacterium tuberculosis HSP70 DNA. At best, Chen *et al.* teaches that the fusion of an HSP DNA to a DNA vaccine, converts a less effective DNA vaccine into one with greater potency against established antigen-expressing tumor cells. In Chen et al., the DNA vaccine is the same substance as the HSP preparation. In contrast, in the presently claimed invention, the vaccine composition and the HSP preparation cannot be the same substance, since the vaccine composition and the HSP preparation do not display the same immunogenicity (in that the HSP preparation "does not display the immunogenicity of the component" of the vaccine composition). In Chen *et al.*, the HSP preparation does display the immunogenicity of the component of the vaccine since it is the component. That Chen's

entire fusion molecule should be considered as the "HSP preparation" as that term is used in the claims is shown by reference to the instant specification at page 14, lines 29-31, where it is made clear that the term HSP preparation is intended to encompass HSPs bound to other molecules. Thus, Chen *et al.* does not teach an HSP preparation that does not display the immunogenicity of the vaccine component, as required by the claims.

In sum, Chen *et al.* does not teach all the limitations set forth in the claims and therefore cannot anticipate the instant claims. Accordingly, in view of the foregoing, Applicant submits that the rejection is in error, and respectfully requests its withdrawal.

REJECTIONS UNDER 35 U.S.C. § 103 SHOULD BE WITHDRAWN

Claims 4, 9, 26-31, 33, 42, 44, and 46 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Chen *et al.* In addition, claims 4, 9, 13, 17, 21, 25-42, and 46 are rejected under USC § 103 as being unpatentable over Yang *et al.* in view of either Suzue *et al.* or Chen *et al.* Applicant disagrees with Examiner for the following reasons.

To find obviousness, there must be a reason or suggestion in the art for carrying out the invention, other than the knowledge learned from the Applicant's disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). Consequently, a finding of obviousness under 35 U.S.C. §103 requires a determination of: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the difference between the claimed subject mater and the prior art; and (4) whether the differences are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere* 383 U.S. 1 (1966).

The Federal Circuit has articulated that the prior art must either expressly disclose every claim limitation or suggest modifications to meet every claim limitation.

Litton Indus. Products, Inc. v. Solid State Systems, 755 F.2d 158, 164 (Fed. Cir. 1985); *see also* MPEP 2143.03. Prior art references may thus be combined to render an alleged invention obvious under 35 U.S.C. § 103, however, the teachings of references can be combined only if there is some suggestion or incentive to do so. *ACS Hospital Systems, Inc. v. Montefiore Hospital*, 732 F.2d 1572, 1575 (Fed. Cir. 1984).

The Federal Circuit has indicated that a *prima facie* case of obviousness requires "objective evidence of record" demonstrating that there is prior art that teaches or suggests combining the asserted references as proposed. *In re Lee*, 277 F.3d 1338, 1341 (Fed. Cir. 2002). The Court has also made clear that the requirement for a showing of the teaching or motivation to combine prior art references must be "clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not evidence." *In re Dembiczak*, 173 F.3d 994, 999 (Fed. Cir. 1999). Furthermore, the motivation to combine references originate from one of three sources: the nature of the problem to be solved, the teachings of the prior art, or the knowledge of persons of ordinary skill in the art. In re Rouffet, 47 U.S.P.Q.2d 1453, 1457-58 (Fed. Cir. 1998).

Moreover, care must be exercised not to use the Applicant's disclosure to fill in the gaps in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985). Thus, Applicant's own teaching in the application in question also cannot constitute a proper basis for formulating obviousness rejections; hindsight reconstruction on the basis of an applicant's disclosure is impermissible. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995); *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995).

With respect to the § 103(a) rejection of claims 4, 9, 26-31, 33, 42, 44, and 46 over Chen *et al.*, the Examiner acknowledges that Chen *et al.* does not teach the administration of the HSP before or after the administration of the vaccine. The Examiner

concludes however, that it would have been *prima facie* obvious to one of skill in the art to attempt different administration methods or regimes, including varying the timing of administration of the HSP relative to the vaccine.

In response, Applicant redirects the Examiner to the discussion *supra*, explaining that Chen *et al.* only teaches the administration of an HSP-vaccine complex, which is an HSP preparation in which the HSP displays the immunogenicity of the vaccine component, *i.e.*, the antigenicity of the papillomavirus E7 antigen. Furthermore, there is no suggestion in Chen *et al.* of administering a DNA vaccine and an HSP in which the DNA vaccine and HSP are separate molecules. As explained above, there is not hint or suggestion in Chen et al. of administering an HSP preparation that does not display the antigenicity of the vaccine component. Thus, the claimed invention is non-obvious over Chen *et al.*

In response to the rejection of claims 4, 9, 13, 17, 21, 25-42, and 46, over Yang *et al.* in view of Suzue *et al.* or Chen *et al.*, Applicant respectfully disagrees that the above combined teachings render the presently claimed invention obvious.

Yang *et al.* reports that vaccines (dendritic cell-based vaccines wherein the dendritic cells have been transfected with a gene encoding human melanoma-associated antigen gp100) are more effective than naked-DNA vaccines at inducing anti-tumor immunity. Yang *et al.* at page 537. Yang *et al.* also reports that vaccines (dendritic cell-based vaccines wherein the dendritic cells have been transfected with a gene encoding human melanoma-associated antigen gp100) are more effective at reducing tumor burden in mice than naked-DNA vaccines. Yang *et al.* at page 537-38. Yang et al. clearly does not teach the administration of a vaccine, and the administration of an HSP preparation wherein the HSP preparation does not display the immunogenicity of the vaccine.

Suzue *et al.* does not cure this deficiency. Suzue *et al.* does not teach the use of an HSP preparation which does not display the immunogenicity of a vaccine component that displays the antigenicity of a cancer cell. Suzue *et al.* reports that heat shock fusion proteins are potent immunogens for eliciting a CD8 cytotoxic T lymphocyte immune response. Suzue *et al.* discloses the use, as an immunogen, of a recombinant heat shock fusion protein containing a large fragment of ovalbumin covalently linked to mycobacterial hsp70. Suzue *et al.* at p. 13181, third paragraph, also refers to the use of gp96-peptide complexes as immunogens. Suzue et al., like Chen *et al.*, thus discloses vaccines that are the same substances as the HSP preparation, and thus, like Chen *et al.*, fails to teach or suggest an HSP preparation that does not display the immunogenicity of the vaccine component. Thus, Suzue *et al.* in combination with Yang *et al.*, does not teach the presently claimed invention.

Chen *et al.* also fails to cure the deficiencies of Yang *et al.* As discussed above, Chen *et al.*, teaches an HSP preparation that does display the immunogenicity of the component of the vaccine since it is the component. Thus, Chen *et al.* does not teach, or even suggest, an HSP preparation which does not display the immunogenicity of the component, since in Chen *et al.* the HSP preparation is the vaccine. Thus, Yang *et al.* in view of Chen *et al.* fails to render the presently claimed invention obvious.

In sum, neither Yang *et al.* nor Suzue *et al.* teach or suggest the methods claimed herein. Accordingly, in view of the foregoing, Applicant submits that the rejection is in error, and respectfully requests its withdrawal.

CONCLUSION

Applicant respectfully requests entry of the foregoing amendment and remarks into the file history of the above-identified application. Applicant believes that each ground

of rejection has been successfully overcome, and that all pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and objections, and allowance of the application, are respectfully requested.

Respectfully submitted,

Date December 23, 2002

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EXHIBIT A
MARKED-UP VERSION OF CLAIMS AMENDED HEREIN
U.S. Patent Application No. 09/693,643
December 23, 2002

4. **(Amended)** A method of treating or [preventing] a cancer in a subject comprising the steps of:

(a) administering to the subject a [vaccine] composition comprising a component that displays the antigenicity of a cancer cell; and

(b) administering to the subject [an amount of] a [heat shock protein] preparation [effective to induce or increase an immune response in the subject to the component], wherein the heat shock protein preparation does not display the immunogenicity of the component.

13. **(Amended)** The method according to claim 4 wherein the heat shock protein preparation comprises heat shock protein-peptide [complexes] complex.

17. **(Amended)** The method according to claim 4 wherein the heat shock protein preparation comprises purified heat shock [proteins] protein.

21. **(Amended)** The method according to claim 4 wherein the heat shock protein preparation comprises heat shock protein-peptide [complexes] complex and purified heat shock [proteins] protein.

25. **(Amended)** The method according to claim 4 wherein the subject is human and the heat shock protein preparation comprises mammalian heat shock [proteins] protein.

42. **(Twice amended)** The method of claim 4 or 25 wherein the vaccine composition is a live vaccine, an inactivated vaccine, an attenuated vaccine, a subunit vaccine, a DNA vaccine, [or] a RNA vaccine, or a tumor antigen vaccine.

44. **(Amended)** The method according to claim 4 wherein the cancer is selected from the group consisting of fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma[;], leukemia[s], [e.g.,] acute lymphocytic leukemia [and], acute myelocytic leukemia, [(]myeloblastic leukemia, promyelocytic leukemia, myelomonocytic leukemia, monocytic leukemia, [and] erythroleukemia [);], chronic leukemia [(], chronic myelocytic leukemia, [(]granulocytic[)] leukemia [and], chronic lymphocytic leukemia[); and], polycythemia vera, lymphoma, [(]Hodgkin's disease lymphoma, [and] non-Hodgkin's disease lymphoma[)], multiple myeloma, Waldenström's macroglobulinemia, and heavy chain disease.